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In the Supreme Court of the United States

OCTOBER TERM, 1968

No. 343

UNITED STATES OF AMERICA, PETITIONER

v.

AN ARTICLE OF DRUG * * * BACTO UNIDISK * * *

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE SIXTH CIRCUIT

BRIEF FOR THE UNITED STATES

OPINIONS BELOW

The opinion of the court of appeals (App. 198–202) is reported at 392 F. 2d 21. The opinion of the district court (App. 186–191) is not reported.

JURISDICTION

The judgment of the court of appeals was entered on March 29, 1968 (App. 203). On June 18, 1968, Mr. Justice Stewart extended the time for filing a petition for a writ of certiorari to and including July 26, 1968 (App. 204). The petition was filed on that date, and was granted on October 21, 1968 (App. 206). The jurisdiction of this Court rests on 28 U.S.C. 1254(1).

QUESTION PRESENTED

Whether the Secretary of Health, Education, and Welfare correctly concluded that discs containing various antibiotic drugs—discs which physicians use to select the antibiotic most appropriate to treat a particular patient—are "antibiotic drugs" under the Federal Food, Drug, and Cosmetic Act, and therefore are subject to the requirement in Section 507 of that Act that, pursuant to regulations of the Secretary, each such drug be tested by batches to insure its safety and efficacy.

STATUTE INVOLVED

The Federal Food, Drug, and Cosmetic Act, 52 Stat. 1040 (1938), as amended, 21 U.S.C. 301, *et seq.*, provides in part:

> *Sec. 201* [*21 U.S.C. (Supp. II) 321*]
>
> For the purposes of this Act—
>
> * * * * *
>
> (g) (1) The term "drug" means (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clauses (A), (B), or (C); but does

not include devices or their components, parts or accessories.

* * * * * * *

(h) The term "device" * * * means instruments, apparatus, and contrivances, including their components, parts, and accessories, intended (1) for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; or (2) to affect the structure or any function of the body of man or other animals.

Section 502 [*21 U.S.C. 352*]

A drug or device shall be deemed to be misbranded—

(l) If it is, or purports to be, or is represented as a drug composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, bacitracin, or any other antibiotic drug, or any derivative thereof, unless (1) it is from a batch with respect to which a certificate or release has been issued pursuant to section 507, and (2) such certificate or release is in effect with respect to such drug: *Provided,* that this paragraph shall not apply to any drug or class of drugs exempted by regulations promulgated under section 507 (c) or (d).

Section 507 [*21 U.S.C. 357*]

(a) The Secretary of Health, Education, and Welfare, pursuant to regulations promulgated by him, shall provide for the certification of batches of drugs composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, bacitracin, or any other antibiotic drug, or any derivative thereof.

A batch of any such drug shall be certified if such drug has such characteristics of identity and such batch has such characteristics of strength, quality, and purity, as the Secretary prescribes in such regulations as necessary to adequately insure safety and efficacy of use, but shall not otherwise be certified. Prior to the effective date of such regulations the Secretary, in lieu of certification, shall issue a release for any batch which, in his judgment, may be released without risk as to the safety and efficacy of its use. Such release shall prescribe the date of its expiration and other conditions under which it shall cease to be effective as to such batch and as to portions thereof. For purposes of this section and of section 502(*l*), the term "antibiotic drug" means any drug intended for use by man [1] containing any quantity of any chemical substance which is produced by a microorganism and which has the capacity to inhibit or destroy microorganisms in dilute solution (including the chemically synthesized equivalent of any such substance).

(b) Regulations providing for such certifications shall contain such provisions as are necessary to carry out the purposes of this section, including provisions prescribing (1) standards of identity and of strength, quality, and purity; (2) tests and methods of assay to determine compliance with such standards; (3) effective

[1] This definition was added by the Drug Amendments of 1962, P.L. 87-781, 76 Stat. 785, to extend the certification controls to all antibiotics intended for human use, as contrasted with drugs solely for veterinary use. H. Rep. 2526, 87th Cong., 2d Sess., October 3, 1962, Conference Report, Statement of Managers on the Part of the House, pp. 21-22; S. Rep. 1744, 87th Cong., 2d Sess., p. 19. See also the Statement by Senator Kefauver, 103 Cong. Rec. 22039, October 3, 1962.

periods for certificates, and other conditions under which they shall cease to be effective as to certified batches and as to portions thereof; (4) administration and procedure; and (5) such fees, specified in such regulations, as are necessary to provide, equip, and maintain an adequate certification service. Such regulations shall prescribe only such tests and methods of assay as will provide for certification or rejection within the shortest time consistent with the purposes of this section.

STATEMENT

On May 25, 1962, the United States District Court for the Eastern District of Michigan ordered the seizure of an interstate shipment of five cases of articles labeled "Bacto-Unidisk" pursuant to a libel filed by the government charging that the articles were composed of antibiotic drugs which were neither certified nor exempted from certification as required by Section 507 of the Federal Food, Drug, and Cosmetic Act, *supra*, and the regulations issued thereunder (21 C.F.R. 147) (App. 5–6). On August 21, 1966, after a trial, the court ruled that the articles were not "drugs" within the meaning of the statute and ordered them returned to the claimant, Difco Laboratories (App. 192–196). The court of appeals affirmed (App. 198–203).

1. BACKGROUND[2]

Antibiotics are chemical substances, produced by various species of microorganisms, which suppress the

[2] In addition to the materials cited therein, the text is derived from Bauer, Kirby, Sherris, and Turck, *Antibiotic Susceptibility Testing by a Standardized Single Disk Method*, 45 American Journal of Clinical Pathology 493, at 493–494, 496 (1966);

growth of other microorganisms and may eventually destroy them. The systematic use of antibiotics as therapeutic agents began in the early 1940's with the advent of penicillin. When of proper potency and free from toxic impurities, penicillin proved useful for treatment of numerous life-threatening infectious diseases. Penicillin was produced by a biological process, however, and was subject to the vagaries inherent in such processes. Moreover, the methods for assaying the potency of penicillin were also biological in nature, and were generally uncertain and variable unless conducted under very carefully controlled conditions. Because of this, and because methods previously developed to assure quality control in the preparation of other drugs were inadequate to deal with a substance having these characteristics, Congress, in Section 507 of the Act, *supra*, directed the Secretary of Health, Education and Welfare to promulgate regulations establishing such standards of identity, potency, quality and purity as are necessary to insure the safety and efficacy of antibiotics for their intended use, and to provide for the certification of batches meeting such standards. See H. Rep. 702, 79th Cong., 1st Sess. (1945), particularly the letter from the Acting Federal

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Petersdorf and Sherris, *Methods and Significance of in Vitro Testing of Bacterial Sensitivity to Drugs*, 39 American Journal of Medicine 766, at 771 (1965); Gould, *The Laboratory Control of Antibiotic Therapy*, 3 Chemotherapia 477, at 478–481 (1961); Second Report of the Export Committee on Antibiotics, *Standardization of Methods for Conducting Microbic Sensitivity Tests*, World Health Organization Technical Report Series No. 210, pp. 12–17 (1961).

Security Administrator recommending the legislation, pp. 10–11.

More than 30 antibiotics are currently listed (21 C.F.R. 145.3). The regulations governing these various antibiotics now cover more than 700 pages in the Code of Federal Regulations, consisting for the most part of highly detailed specifications and standards designed to assure the safety and efficacy of each of the antibiotics in each of its various forms (21 C.F.R. 141.1–148z.4).

With the development of the many forms of antibiotics (including some which present a serious risk of undersirable and sometimes dangerous side effects, when administered to some patients), it became important in medical practice to have a screening test which would provide the physician with an accurate estimate as to which among the several available antibiotics would be likely to be effective against his patient's infecting organism. A diffusion test, using antibiotic sensitivity discs, soon became the most widely employed screening method. In this test, a specimen of the affected fluid (blood, spinal fluid, sputum, urine, pus, etc.) is drawn from the patient. The specimen is applied upon an agar culture medium contained in a small glass dish, and is incubated for a period of hours. Sample cultures (isolates) of the infecting microorganism which have grown upon the surface of the agar are then placed in a liquid solution and applied upon a second agar culture medium. Dry paper discs, each of which has been impregnated with a certain quantity of a specific antibiotic, are gently pressed upon the surface of the inoculated agar

and the isolate is then incubated for six to eighteen hours in contact with the discs.

During incubation, the antibiotics disseminate outward, forming circular zones around each of the paper discs. In the zones around the discs which were impregnated with a particular antibiotic to which the infecting microorganism is sensitive, no new culture of the microorganism isolate will grow, leaving a clear circle on the agar medium; in the zones around discs which were impregnated with an antibiotic to which the microorganism is resistant, the isolate will grow, leaving little or no clear area. From the presence and size of the clear zones of inhibition around the various discs, the microbiologist is able to advise the physician which of the antibiotics have demonstrated the greatest effectiveness against the infecting mircoorganism.

The entire process usually takes approximately 24 to 36 hours. In many situations the test is modified to the extent that the infecting microorganism is not first isolated; the original specimen from the patient is incubated on the agar medium while in contact with the antibiotic-impregnated discs. In such cases, usable results may be obtained in as little as eight hours.

In September 1960, after notice (25 Fed. Reg. 3084) and an opportunity for public participation, the Commissioner of Food and Drugs, under authority delegated by the Secretary of Health, Education, and Welfare, promulgated regulations requiring preclearance and batch certification of antibiotic sensitivity discs and of dry powders of antibiotics used for sensitivity testing in the diagnosis or treatment of disease (25 Fed. Reg. 9369). The order recited

that sensitivity discs initially had been exempted from certification requirements, but that, following "numerous complaints by the medical profession, hospitals, and laboratory technicians, the Food and Drug Administration made an extensive survey of the conditions surrounding the production and marketing" of discs and found them unreliable in their statements of potency with resultant impairment of their safety and efficacy (25 Fed. Reg. 9370). It was therefore deemed "vital for the protection of the public health" (*ibid.*) to adopt regulations requiring batch certification of antibiotic sensitivity discs.

Six manufacturers of antibiotic sensitivity discs and powders, including Difco Laboratories, the claimant herein, filed objections to the announced regulations prior to their effective date, but the Commissioner found the objections insufficient to require a hearing (26 Fed. Reg. 2596–2597). No judicial review of the promulgating order, as authorized by 21 U.S.C. 357(f) and 371(f), was sought by the manufacturers. The regulations became effective on March 28, 1961, and are published at 21 C.F.R. 147.

2. THIS LITIGATION

This case arose on May 25, 1962, as an *in rem* seizure proceeding against an interstate shipment of a number of cases of antibiotic sensitivity discs bearing the trade name "Bacto-Unidisk." The libel alleged that the Bacto-Unidisk (1) was a "drug" within the meaning of the Act, (2) was composed of specific antibiotic drugs, and (3) was neither certified nor exempted from certification, as required by Section

507 of the Act and the regulations issued thereunder (App. 5–6). Difco Laboratories, the manufacturer of the discs, appeared as claimant and admitted the allegations, except that it denied that the articles were "drugs," and thus that they were subject to the batch certification requirements under the statute (App. 7, 28–29; see App. 8–20). When the case came to trial in May 1965,[3] the only substantive question was whether the articles were "drugs," within the meaning of Section 201(g) of the Act, *supra*.[4] This issue arises because Section 507(a) of the Act, *supra*, defines "antibiotic drug" as "any drug * * *" and thus depends for its applicability on the Act's general definition of "drug" in Section 201(g).

The Bacto-Unidisk is a flat ring of three-sixteenths inch wide paper with an overall diameter of three and five-sixteenths inches. Extending inward from the ring are eight evenly-spaced protrusions each about three-eighths of an inch long. Seven of the protrusions terminate in one-quarter inch diameter circles; one terminates in a one-quarter inch square. Each of the one-quarter inch circles is impregnated with a different antibiotic, the name of which is printed on the outer ring at the base of the protrusion. The square is impregnated with a sulfonamide (sulfadiazine), a chemical which is used for therapeutic purposes but which is

[3] Cross motions for summary judgment were denied on April 6, 1965 (App. 29–31).

[4] The government contended in the courts below that the claimant was barred from raising this issue by its failure to seek judicial review of the order promulgating the regulation, but that issue was not raised in the petition for certiorari and the government does not in this Court challenge the claimant's standing to raise the statutory issue in this litigation.

not an antibiotic. The general appearance is that of a small paper wheel having eight spokes, with the central section (the hub and most of each spoke) punched out (Libelant's Exhibit 1; App. 34–35, 180–185).

The labeling enclosed with each carton of Bacto-Unidisks states that the disks contain standardized amounts of eight therapeutic agents, that they are "especially valuable in selecting the drug effective against chronic or persistent infections refractory to primary therapy", and that they are "recommended as a rapid, practical, clinically accurate and inexpensive means of determining the relative sensitivity of microorganisms to these therapeutic agents" (Libelant's Exhibit 1; App. 34–35, 180–185).

In use, the Bacto-Unidisk is employed in the same manner as other antibiotic sensitivity discs, following the general procedure described above (App. 8–20, 39, 42–43, 45–47, 183–185). The attachment of the individual discs to a common paper ring is designed only as a matter of convenience. It is undisputed on this record that the results of sensitivity testing guide the physician in his selection of a treatment agent, and help him rule out agents that are not effective or which are less effective against his particular patient's infection (App. 43, 47, 48, 51, 54, 60–61, 64–67, 69, 75, 77, 79, 104, 120, 122, 124, 127, 131, 136, 142–143).

Three expert witnesses, called by the government, Dr. Joseph Paul Truant, Chief Bacteriologist, Henry Ford Hospital, Detroit (App. 35, 82), Dr. Charles K. Wolfe, an internist specializing in infectious diseases

at the University of Illinois Medical School (App. 62), and Dr. Albert Martin Lerner, Chief of Infectious Diseases, Detroit Receiving Hospital and Associate Professor of Medicine, Pathology and Microbiology at Wayne State University School of Medicine (App. 134), testified that the Bacto-Unidisk was used as a guide in the treatment, cure, and prevention of disease (App. 47–48, 64, 67, 69, 75, 136, 142–143). Dr. Lerner said: "It is impossible to deal with a sick patient with an infection without dealing and grappling with disks and the results of these disks" (App. 136).

Claimant's expert medical witness, Dr. Chester S. Keefer, Professor of Medicine Emeritus, Boston University School of Medicine, a leader in the early development of antibiotic therapy, classified the disc as a laboratory agent (App. 107, 116). He took the view that medical diagnosis is an art in which the disc plays only a part, and that "without regard to any statutory terms or definitions," a drug "in the medical sense is a chemical or combination of chemicals that is used for the treatment of patients" or for "relief of symptoms" by local application, orally, or by injection (App. 123). He said that he did not know of any substance, from a medical standpoint, that would be classified as a drug which would not be used in that manner (App. 123). Thus, he concluded that the Bacto-Unidisk is not a drug in the medical sense, as he understood the term to be used. Nonetheless, Dr. Keefer testified that sensitivity discs are used in the course of treating patients with complicated infections who are not responding to a

broad spectrum antibiotic, and that, as a result of the disc tests, the treatment is frequently changed to another antibiotic (App. 123–124).[5]

In its memorandum opinion (App. 186–191) the district court held that even though a "literal reading" of Section 201(g)(2) "clearly has application to the article libeled herein" (App. 190), and "despite the fact that drugs are contained in the article," the Bacto-Unidisk does not come within the purview of the definition of "drug" for the reason that "no part of this article is administered to man or other animals, either internally or externally, and that its sole function is to provide medical doctors with information for use by them as guidelines" (App. 190–191). The court suggested, without deciding, that the discs would more appropriately be classified as "devices" under Section 201(h) of the Act, *supra* (App. 190).

The court of appeals affirmed, stating that the sole function of the discs is to furnish doctors with information which enables them to treat diseases previously diagnosed; that the discs have nothing to do with diagnosis or prevention of disease; and that, although the discs aid physicians in the determination of what antibiotic to use for the cure, mitigation or treatment of disease, Congress did not intend to apply the statutory phrase "intended for use in the * * * cure, mitigation, [or] treatment" in such an indirect manner (App. 199–200).

[5] The claimant's other witnesses established that antibiotic discs are not listed in the United States Pharmacopoeia or the National Formulary, and thus do not come within that portion of the definition of "drug" in Section 201(g)(1)(A).

SUMMARY OF ARGUMENT

Because of the peculiar scientific properties of antibiotic drugs, Section 507 of the Federal Food, Drug, and Cosmetic Act, *supra*, requires the batch testing of such drugs in order adequately to insure their safety and efficacy of use. Under authority delegated by that provision, the Secretary of Health, Education, and Welfare has determined, in a rule-making proceeding, that this batch-testing requirement applies to antibiotic sensitivity testing discs, which are impregnated with various antibiotic drugs and which are used to select the antibiotic most appropriate for treatment of a particular patient. This administrative determination serves the purpose of Section 507 by providing needed assurance that patients will get the therapeutic benefit intended when physicians prescribe antibiotic drugs.

The Secretary correctly interpreted the Act as authorizing the application of the batch-testing requirement to antibiotic discs. That interpretation is consistent with the language and legislative history of the Act and is in furtherance of the statutory purpose. This important public health legislation is properly interpreted functionally, so as to afford the public the statutory protections that are scientifically pertinent to the characteristics of the particular article at issue and to the medical use for which it is intended. The contrary interpretation by the courts below—which turns on usage of the word "drug" outside the statute, without regard to the statutory definition or statutory purpose—erroneously deprived

the public of the only statutory protection which is adequate to assure that antibiotic sensitivity discs will be safe and efficacious in use.

ARGUMENT

I

BATCH TESTING OF ANTIBIOTIC DISCS ACCORDS WITH THE PURPOSE OF CONGRESS, EXPRESSED IN SECTION 507 OF THE ACT, TO ASSURE THAT ANTIBIOTIC DRUGS USED IN THE TREATMENT OF DISEASE HAVE THE QUALITIES NECESSARY "TO ADEQUATELY INSURE SAFETY AND EFFICACY OF USE"

A. A PRINCIPAL PURPOSE OF SECTION 507 IS TO INSURE EFFICACY OF USE OF ANTIBIOTIC DRUGS

Section 507 of the Federal Food, Drug, and Cosmetic Act, *supra*, gives the Secretary of Health, Education, and Welfare the duty to provide by regulation "for the certification of batches" of antibiotic drugs to assure that they have such characteristics of strength, quality, and purity as are necessary "to adequately insure safety and efficacy of use."

As set forth in the statement, treatment of disease by antibiotic therapy has become increasingly important in recent years. One leading work on the subject[*] has said,

> The medical, public health, and economic aspects of antibiotics are difficult to overestimate, and the years elapsing since their introduction into therapy have witnessed dramatic reductions in the incidence of, and morbidity and mortality due

[*] Goodman & Gilman, *The Pharmacological Basis of Therapeutics*, 3d Ed. 1965, p. 1172.

to, a number of infectious diseases heretofore unresponsive to chemotherapy.

Because of the biological process by which antibiotic drugs are produced, variations in the products may easily occur and are difficult to detect. As a result antibiotic drug certification began in September 1943, when penicillin first became available as an anti-infective agent for use by the Armed Forces. (App. 114–115.) In 1945, when the wartime controls were relaxed, Congress first enacted Section 507 as an amendment to the Federal Food, Drug, and Cosmetic Act to impose this type of regulatory control. P.L. 79–139, 59 Stat. 463. While this provision initially applied only to penicillin, as new antibiotics having similar characteristics (see *supra*, p. 6) came into use, the requirement was extended: to streptomycin in 1947,[7] to aureomycin (chlortetracycline), chloramphenicol and bacitracin in 1949,[8] and to all other antibiotics for human use in 1962.[9]

Testifying in support of the 1962 Amendments to expand the certification program, the then Secretary of Health, Education, and Welfare, Mr. Ribicoff, said:

> These antibiotic drugs are the drugs of first choice in treating life-threatening infectious conditions. They affect a larger part of the population than any other drug used in similar conditions. Since they are employed in conditions where even minor delays in effective treatment may result in death, it is essential

[7] P.L. 16, 61 Stat. 11.
[8] P.L. 164, 63 Stat. 409.
[9] P.L. 87–781, 76 Stat. 785–787.

> that they be fully potent, absolutely safe, and properly labeled. It would be in the public interest and in the interest of good medical practice to require certification of all antibiotics, as provided in S. 1552.

Hearings before the Subcommittee on Antitrust and Monopoly, Committee on the Judiciary, United States Senate, 87th Cong., 1st Sess., September 13, 1961, p. 2590.

Certification requires that the sponsor of an antibiotic drug develop and present to the Secretary of Health, Education, and Welfare scientific data derived from preclinical and clinical investigations to establish the conditions of its safe and effective use. The Secretary then promulgates regulations, based upon the scientific data, establishing such standards of identity, strength, quality, and purity as are necessary adequately to insure safety and efficacy of the antibiotic for its intended use. Thereafter the sponsor submits to the government samples from each production batch of the antibiotic. These are examined and tested in government laboratories for compliance with the standards and with packaging, labeling, and advertising requirements. 21 CFR 146.2–146.4, 146.10, 147. In short, certification is a system of preclearance involving advance approval of the drug and its packaging, promotion, and labeling to assure safety and effectiveness in use.

The requirement for safety and "efficacy of use" means that antibiotic drugs are not, and cannot properly be, tested in and of themselves, separate and apart from the form in which they are used. If an anti-

biotic is used in a tablet or hypodermic dose, it is necessary to test the tablet or the liquid for assurance that it has its declared potency and will dissolve properly or be transmitted to the patient's bloodstream to treat his infection. In other words, batch-testing is not a theoretical, academic exercise; it is a method of assuring that, when the physician prescribes a particular antibiotic, the patient gets the treatment which the physician intended.

B. BATCH TESTING OF ANTIBIOTIC DISCS IS IN ACCORD WITH THE PURPOSE OF THE ANTIBIOTIC AMENDMENTS

Batch testing of antibiotic discs serves the purpose of the antibiotic drug amendments to protect the public health by ensuring that the patient will get the therapeutic benefit intended when a physician prescribes a particular antibiotic drug.

1. The rational use of antibiotics depends upon laboratory testing of the infecting organism to determine which drug or drugs may be effective against that organism. Goodman and Gilman, in their book, *The Pharmacological Basis of Therapeutics* (3d ed. 1965) state, at page 1174:

> The sensitivities of bacteria to various antimicrobial agents are usually determined by microbiological methods. The most accurate technic for use in the routine diagnostic laboratory involves inoculation of the organism being tested into a liquid culture medium in test tubes containing serial dilutions of the drug. After a suitable period of incubation, the lowest concentration of antibiotic inhibiting growth of the bacteria is expressed as the "sen-

sitivity". A more rapid method involves the use of commercially available filter-paper discs infiltrated with specific quantities of the drugs. These are placed on the surface of agar plates over which a culture of the organism being examined has first been streaked. Although this is a relatively crude procedure, the accuracy of which may be influenced by pH, size of inoculum, thickness of the agar medium, temperature of incubation, and the accuracy of the stated quantity of drug present in the paper disc, it is of practical clinical importance in indicating which antibiotic to employ and the general level of dose required to produce a therapeutic effect.

Antibiotic sensitivity discs and sensitivity testing procedures were developed commercially in 1949 or 1950 (App. 126) to provide such a rapid screening test. In the beginning, only three antibiotic drugs were involved. As new antibiotics were introduced into clinical practice, new discs were developed to facilitate the safe and effective use of these new therapeutic agents. Today, approximately 82 percent of the hospitals and clinical laboratories in the United States conduct senstivity tests prior to the initiation of antibiotic therapy,[10] and almost all antibiotic sensitivity

[10] Isenberg, *A Comparison of Nationwide Microbial Susceptibility Testing Using Standardized Discs*, 1 Health Laboratory Science 185, 186 (1964).

Such testing not only serves to assure that the particular patient will receive an appropriate and effective antibiotic, it also helps to prevent the selection of unneeded special-purpose antibiotics prone to engender the development of resistant strains of infecting organisms. This has led the Expert Committee on

testing is carried out by the use of commercially prepared antibiotic impregnated discs.[11] Extensive bacteriological investigations have been conducted to validate the disc method of sensitivity testing, and it is accepted today that the results yielded by properly prepared discs, properly interpreted, are reliable guides to antibiotic therapy.[12]

2. Critical to the reliability, safety and effectiveness of the antibiotic discs are assurance of identity, strength, quality and purity of the antibiotic drugs used to impregnate the disc; proper packaging to prevent deviations from those standards before use;

Antibiotics of the World Health Organization to conclude that sensitivity testing is "essential * * * for preserving the efficacy of this important group of therapeutic substances" by limiting their use to the special circumstances in which they are uniquely effective. Second Report of the Expert Committee on Antibiotics, *Standardization of Methods for Conducting Microbic Sensitivity Tests*, World Health Organization Technical Report Series No. 210, p. 3 (1961).

[11] Rose and Berky, *A Quality Control System for Disk Antibiotic Testing*, 48 American Journal of Clinical Pathology 200 (1967).

[12] See, generally, Truant, Bolin, and Mullins, *Evaluation of Susceptibility Testing Procedures with Single and Multiple Antibiotic Discs*, Antimicrobial Agents and Chemotherapy, 384, 393–394 (1964); Bauer, Kirby, Sherris, and Turck, *Antibiotic Susceptibility Testing by a Standardized Single Disk Method*, 45 American Journal of Clinical Pathology 493, 496 (1966); Rose and Berky, *A Quality Control System for Disk Antibiotic Testing*, 48 American Journal of Clinical Pathology 200, 212–213 (1967).

and proper labeling to provide the physician information as to how long the disc may be expected to be reliable (an expiration date) and how the results of disc testing are to be interpreted in applying them to the clinical situation.[13]

Excessive potency, for example, may falsely indicate that the patient's infection is susceptible to treatment with that particular antibiotic.[14] Failure to package the disc properly with a desiccant to prevent moisture uptake may substantially affect the diffusion of the antibiotic drugs from the disc into the bacterial growth medium.[15] Labeling may fail to provide proper information for interpreting the results of the disc test. Just as a patient's life may be endangered by an improper tablet, a patient's life may well be jeopardized by a disc which contains, *e.g.*, an excess in potency with too rapid diffusion, giving a false reading

[13] See, *e.g.*, Second Report of the Expert Committee on Antibiotics, *Standardization of Methods for Conducting Microbic Sensitivity Tests*, World Health Organization Technical Report Series No. 210, pp. 12–13 (1961); Truant, Bolin, and Mullins, *Evaluation of Susceptibility Testing Procedures with Single and Multiple Antibiotic Discs*, Antimicrobial Agents and Chemotherapy 384 (1964); Bauer, Kirby, Sherris, and Turck, *Antibiotic Susceptibility Testing by a Standardized Single Disk Method*, 45 American Journal of Clinical Pathology 493, 496 (1966).

[14] See, *e.g.*, Rose and Berky, *A Quality Control System for Disk Antibiotic Testing*, 48 American Journal of Clinical Pathology 200, 204 (1967); Murayama, *Fundamental Study on the Disc Method of Antibiotic Sensitivity Test*, 12 Journal of Antibiotics, Ser. A, 263 (1959).

[15] See Ostrander and Griffith, *An Evaluation of Different Types of Paper Concerning Their Suitability for Sensitivity Discs*, Antibiotics Annual 1958–1959, p. 813, at p. 817; Griffith and Mullins, *Drug Resistance as Influenced by Inactivated Sensitivity Discs*, 16 Applied Microbiology 656 (1968).

of sensitivity to that particular antibiotic. False readings result in misinformation to the physician, with the result that the patient is not treated properly.[16]

Indeed, the labeling for most of the antibiotics listed in 21 C.F.R. 145.3—and thus available for marketing—contains directions that the drug is to be used against known sensitive organisms, or after antibiotic sensitivity testing of the patient's organisms or bacteriologic tests of the sort provided by the sensitivity units. See the *Physicians' Desk Reference to Pharmaceutical Specialties and Biologicals* (1968). The directions for Unipen (p. 1244), for example, state, "Therapy with this product, like that with all other potent antimicrobials, should always be accompanied by appropriate bacteriologic culture studies." The revised monograph for Lincocin (Supplement B, p. B27) tells the physician to "[d]o in vitro culture and susceptibility studies in conjunction with Lincocin therapy." And the revised labeling requirements for chloramphenicol, one of the antibiotics in the Bacto-Unidisk, warn that because of its dangerous and sometimes fatal side effects, "[s]ensitivity testing is essential to determine its indicated use."[17]

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[16] The result of such misinformation can be to "deny the patient the use of a life-saving drug" or to give the patient "a drug that would have little or no therapeutic value to him," thus presenting a "serious health hazard." Greenberg and Fitzpatrick, *On the Control of Antibiotic Discs in Canada*, 79 Canadian Medical Association Journal 383 (1958).

[17] The prescribing directions for this antibiotic were revised in May 1968 by a notice to all physicians in the United States, subsequently published at 33 Fed. Reg. 15566 (October 18, 1968), which stated: "Chloramphenicol is an antibiotic that is clinically useful for, *and should be reserved for*, serious infec-

The reliability of antibiotic sensitivity testing affects both the safety and the effectiveness of the patient's treatment. This is true whether the disc is used before or concurrent with the initiation of therapy. The record is clear that the results of the tests performed with the disc are used by the physician as a guide to his selection of the most appropriate antibiotic for treatment of his patient's infection (*e.g.*, App. 43, 47, 51, 60, 64–65, 75, 79, 104, 120, 136, 142–143). In fact, as a result of the test with the disc, the antibiotic being given the patient may be switched at a critical point when he is not responding to the primary therapy (App. 61, 123–124, 127, 131, 142–143).

Proper selection of a safe and effective drug in treating infections, particularly when the infection is refractory and life-threatening, thus depends in substantial measure upon the reliability of antibiotic discs, such as the Bacto-Unidisk, to aid the physician in promptly identifying the drug that is best for ad-

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tions caused by organisms susceptible to its antimicrobial effects when less potentially hazardous therapeutic agents are ineffective or contraindicated. Sensitivity testing is essential to determine its indicated use, but may be performed concurrently with therapy initiated on clinical impression that one of the indicated conditions exists (see 'Indications' section)." (Emphasis in original.) Under "INDICATIONS," the physician is advised that while chloramphenicol "MAY BE CHOSEN TO INITIATE ANTIBIOTIC THERAPY ON THE CLINICAL IMPRESSION THAT ONE OF THE CONDITIONS * * * [LISTED] IS BELIEVED TO BE PRESENT; IN VITRO SENSITIVITY TESTS SHOULD BE PERFORMED CONCURRENTLY SO THAT THE DRUG MAY BE DISCONTINUED AS SOON AS POSSIBLE IF LESS POTENTIALLY DANGEROUS AGENTS ARE INDICATED BY SUCH TESTS." (Emphasis in original.)

ministration to his critically ill patient. As one of the witnesses stated (App. 67):

> I think the antibiotic choice is the thing I particularly used it for, and the reason I use antibiotics is to effect a cure.

In short, the Bacto-Unidisk is intended to be, and is, used in the course of treatment of disease.

3. Batch testing of discs is as important to assuring the safety and efficacy of use of antibiotic drugs as batch testing of tablets, hypodermic dosages, etc. As discussed above, all the qualities which led Congress to require batch testing—the importance of the drug, the variations resulting from biological processes, the need to have the drug in a proper medium—apply as fully to the antibiotics in a disc as to antibiotics in a tablet.

Experience has shown that batch certification is the only practical means of providing assurance of disc reliability. Since the initiation of certification requirements, commentators have acclaimed the step and noted that the certified discs have proven reliable in clinical use.[18] Prior to the promulgation of the certification requirements, however, the Food and Drug Administration's survey which preceded its action in requiring certification of antibiotic discs established that unreliable discs were then being marketed.

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[18] *E.g.*, Griffith and Mullins, *Drug Resistance as Influenced by Inactivated Sensitivity Discs*, 16 Applied Microbiology 656, 658 (1968); Truant, Bolin, and Mullins, *Evaluation of Susceptibility Testing Procedures with Single and Multiple Antibiotic Discs*, Antimicrobial Agents and Chemotherapy 384 (1964).

25 Fed. Reg. 9370. A Canadian survey had shown that discs manufactured in the United States not only were unreliable, but that the assayed content of antibiotics "rarely correspond[ed] to the labeled potency."[19] The commercially available discs were found to vary from 2 percent to 400 percent of their labeled potency, and discs were occasionally found to contain degradation products and traces of antibiotics other than the ones specified.[20]

The Pharmaceutical Manufacturers Association was aware of, and concerned about, the problems.[21] Papers from the academic community noted the serious difficulties of obtaining meaningful information from the routinely used disc tests.[22] Indeed, the problem of disc reliability and disc standardization was of world-wide concern.[23] The Pasteur Institute exercised control over

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[19] Branch, Starkey, Power, and Greenberg, *Problems of Standardization of Manufactured Dry Penicillin Sensitivity Discs*, Antibiotics Annual, 1956–1957, p. 898, at p. 904.

[20] Greenberg, Fitzpatrick and Branch, *The Status of the Antibiotic Disc in Canada*, 76 Canadian Medical Association Journal 194 (1957); Greenberg and Fitzpatrick, *On the Control of Antibiotic Discs in Canada*, 79 Canadian Medical Association Journal 383 (1958).

[21] Gerwe, *Problems Encountered in the Manufacture of Commercial Sensitivity Discs*, Antimicrobial Agents Annual 1960, p. 465. Dr. Gerwe noted that the prescribing physician "has every right to demand that the results obtained be reliable. We are dealing with human lives and we should take any step necessary to better the precision of this test" (*id* at 466).

[22] *E.g.* Branch, Starkey, Power, and Greenberg, *Problems of Standardization of Manufactured Dry Penicillin Sensitivity Discs*, Antibiotics Annual 1956–1957, p. 898.

[23] Branch, Starkey, and Power, *The International Situation with Regard to the Use of Discs for Antibiotic Sensitivity Tests*, Antibiotics Annual, 1958–1959, p. 833.

antibiotic discs sold in France.[24] Canada began to require certification of antibiotic discs in 1958.[25] And in 1961, the World Health Organization recommended that "each government should ensure some system of control over the quality and particularly the antibiotic content of such commercially prepared discs."[26]

Expressions of similar concern about the standardization and reliability of antibiotic discs led to the administrative study which resulted in promulgation of the regulation requiring batch certification of antibiotic sensitivity discs (see Statement, *supra*, p. 9). That study resulted in an administrative determination, which was not challenged by judicial review of the rule-making proceeding, that results yielded by sensitivity tests with discs impregnated with an improper amount of an antibiotic drug, or with discs which did not properly diffuse their antibiotic drugs into the bacterial growth media, were posing a real danger of improper and ineffective therapy with the wrong drug at a critical stage of the patient's course of treatment.

Moreover, the government established at the trial of the present case that there is an important medical need for the certification of antibiotic discs because of the danger to patients of basing treatment upon results drawn from unreliable sensitivity units.

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[24] See Branch, Starkey, Power, and Greenberg, *supra*, at 904.

[25] Trade Information Letter No. 164, dated November 3, 1958, of the Department of National Health and Welfare, Canada.

[26] Second Report of the Expert Committee on Antibiotics, *Standardization of Methods for Conducting Microbic Sensitivity Tests*, World Health Organization Technical Report Series No. 210, p. 13 (1961).

Dr. Truant testified: that "false readings" would be obtained from improperly prepared discs and that the physician consequently "would not treat the patient properly" (App. 83); that poor standardization would result in production of discs "of poor quality, which would give misinformation" to the laboratory and the clinician (App. 84); and that while he could not put his finger on a specific example in which a physician had been misled to the detriment of a patient, he could "recall that there were a number of instances brought to my attention by individuals in the infectious disease department." (App. 93).

Dr. Lerner was asked on cross-examination whether he thought "the public health was involved" in disc reliability. He replied that he did (App. 141). While he personally had not seen a case of patient harm from a faulty disc, he had on some occasions discarded disc data as unreliable because it was inconsistent with other information concerning the patient's condition (App. 141). Dr. Lerner was asked on direct examination about the importance of disc standardization and reliability. He answered, "I feel that it is vital" (App. 139). Hospital laboratories, he said, were unable to test discs for performance, and thus had to rely upon the label representations as to their composition and performance (App. 139–140).

The physician on the front line of clinical practice simply has to accept the discs as having their professed identity, strength, and quality, and as suitable to yield the results claimed in their labeling. The physician does not have the time, the knowledge, the facilities, or the experimental patients needed to test the discs

for potency and performance before using them to determine the sensitivity of his patient's infection to the array of antibiotic drugs packaged on the disc (App. 89, 139–140).

The physician is told repeatedly (see *supra*, p. 22) to do sensitivity testing before or while treating with an antibiotic to assure that the patient's infection is sensitive to the antibiotic he has chosen. Both the physician and the patient can be misled and harmed, even though there is assurance that the capsule, pill or injection is potent and pure, if the sensitivity unit does not reliably give the same sort of assurance that the antibiotic chosen is the proper one. Batch testing of antibiotic discs serves the function for which batch testing of antibiotic drugs was designed—to assure that antibiotic drugs administered to patients are safe and effective in use.

II

THE SECRETARY PROPERLY INTERPRETED THE ACT AS AUTHORIZING THE APPLICATION OF THE BATCH TESTING REQUIREMENT TO ANTIBIOTIC DISCS

1. The courts below did not, essentially, dispute either the need or the desirability of batch testing of antibiotic discs. Nor did they find that such testing would be incompatible with the purposes of Section 507 of the Act. Their holding is based on the view that, whether scientifically needed or not, batch testing of the discs cannot be required by regulation because the Act authorizes the Secretary to impose

such requirement only for "drugs" and, in their view, the antibiotic discs are not "drugs."

Despite the contrary suggestion by the court of appeals (App. 199–200), it is, we submit, clear, as the district court acknowledged (App. 190), that the discs fall within the literal definition of "drug" in Section 201(g) as "articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease." While the disc does not itself make a diagnosis or treat the patient, it plays an essential role in the selection of an appropriate remedy for serious disease. As a result of information as to the inhibiting action of the particular drug on the patient's particular infectious microorganisms, the infection is diagnosed as one sensitive to a particular antibiotic, and the patient is treated with that particular drug. This is certainly a use in the diagnosis and treatment of disease.

The more substantial question in this case is how to draw the line between "drug" as defined in Section 201(g) and "device" which is defined ~~in almost~~ identical terms in Section 201(h) as "instruments, apparatus, and contrivances * * * intended (1) for use in the diagnosis, cure, mitigation, treatment, or prevention of disease * * *." The answer to that question, we think, was given by this Court, in dealing with a similar statutory problem, in *Securities and Exchange Commission* v. *Ralston Purina Co.*, 346 U.S. 119, 124–125. There, in interpreting the statutory exemption from registration for a private offering of stock, the Court said that the "natural way to interpret the private offering exemption is in light of the statutory

purpose." Finding that it was the congressional intent to exempt transactions as to which there was no practical need for the statute's application, the Court ruled that the interpretation of the exemption "should turn on whether the particular class of persons affected needs the protection of the Act." Applying this standard, the Court held, without any reference to usage of the term "public offering" outside the statute, that the company's offering of treasury stock to its "key employees" was a "public offering" subject to the provisions of the Securities Act because the employees had not been "shown to be able to fend for themselves * * *" (*ibid.*).

There is even more reason in the present case than in *Ralston Purina* to be guided by the policy of the statute, and to eschew reference to usage outside the statute,[27] in construing the statutory term at issue. The term "public offering" was nowhere defined in the Securities Act (see 346 U.S. at 122). Here the word "drug" is a statutory term of art, defined in Section 201(g) "[f]or the purposes of this Act", and the discs do, as noted above, fall within the literal terms of the statutory definition.

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[27] The classification of discs as drugs is not as contrary to common medical usage as the district court seemed to believe. "Drug" is defined in Dorland's *Illustrated Medical Dictionary*, 24th Ed., p. 449 (1965), as: "Any chemical compound or any non-infectious biological substance, not used for its mechanical properties, *which may be* administered to or *used* on or *for patients*, either human or animal, *as an aid in the diagnosis, treatment* or prevention of disease or other abnormal condition, for the relief of pain or suffering, or to control, or improve any physiological or pathological condition." (Emphasis added.) This "medical" definition is not dissimilar to that in Section 201(g).

Since the literal terms of the definitions of drug and device overlap, the "natural way" to draw the line, as *Ralston-Purina* explained, "is in light of the statutory purpose." The qualities of antibiotics which led Congress to impose the requirement of batch testing are the same whether the drug is used for a pill, for a hypodermic injection, or as a test to determine what pill or injection to administer. The need for assurance as to quality and potency is essentially the same whether the antibiotic is used on a disc or in a pill or injection. Not only are physicians equally unable to make tests to determine potency, etc., whether the antibiotic is used in a pill or injection or on the disc, but patients—the class of persons that the Act is designed to protect—will derive little benefit from the Act's purpose of assuring that the antibiotic drugs administered to them are safe and properly potent if unreliability of the antibiotic sensitivity discs results in administration of the wrong drug or the wrong amount of drug to them.

In short, the whole purpose of batch testing of antibiotics for safety and efficacy of use applies to the discs of antibiotics. It was, therefore, entirely reasonable for the Secretary to conclude that the discs are drugs under Section 201(g), subject to the batch testing requirements of Section 507.[28]

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[28] Sensitivity discs and sensitivity tablets are classified as "drugs" under Canadian law and regulations. Their Food and Drugs Act defines "drug" and "device" in language similar to that involved in this case. Food and Drugs Act, 1953, 1-2 Eliz. II, c. 38, § 2(e) and (f) (Can.). Pursuant to authority granted by that Act (Section 24), the Governor General in Council, on the recommendation of the Minister of National Health and

2. This interpretation of the statute accords with the settled principle that the Federal Food, Drug, and Cosmetic Act is properly given a broad construction in accord with its purpose to protect the public health. *United States* v. *Sullivan*, 332 U.S. 689. This Court's decisions in *United States* v. *Coca Cola Co.*, 241 U.S. 265, and *62 Cases of Jam* v. *United States*, 340 U.S. 593, 596, have emphasized that it is within "the right and the wisdom" of Congress to provide its own glossary of terms and definitions in the Federal Food, Drug, and Cosmetic Act, and that the judicial function is to apply what the Congress has written. The fundamental error of the courts below lies in their application of what they believed to be the common medical usage of the term "drug" to a complex, technical, regulatory scheme designed for protection of the public health, without regard to either the statutory definition of the term or the purpose of the statute.

The more reasonable approach, in accord with the principles laid down by this Court, is that taken by the Court of Appeals for the Second Circuit in *AMP, Inc.* v. *Gardner*, 389 F. 2d 825, 830 certiorari denied *sub. nom. AMP, Inc.* v. *Cohen*, No. 86, this Term (Oct. 14, 1968), which rejected the idea that this important public law was "restricted to products commonly called "drugs'." Long before that, the Court of Appeals for the Fifth Circuit, interpreting the "drug" definition of the 1906 Food and Drugs Act, rejected as "entirely too narrow" a contention that spring water offered

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Welfare, issued regulations in 1958 which categorized antibiotic sensitivity discs as drugs and provided for their standardization. Food and Drug Regulations, C. 05.061–C. 05.067 (Can.).

for use in treating disease could not be regarded as a "drug" because dictionaries and pharmacopoeias did not so define the term. *Bradley* v. *United States*, 264 Fed. 79, 81. The Act is properly applied functionally to afford the public the protections of the statute that are scientifically pertinent to the characeristics of the particular article at issue and to the medical use for which it is intended. Since batch testing of discs clearly serves the purposes of protecting the public and since the discs do fall within the literal language and evident purpose of Section 507, the Secretary properly directed that they be subject to batch testing.

3. There is nothing in the legislative development of the definition of "drug" that discloses a congressional intent to preclude the application of the batch-testing requirement to articles like antibiotic discs, which are literally within its terms.

The 1906 Food and Drugs Act defined "drug" to include "all medicines and preparations recognized in the United States Pharmacopoeia or National Formulary for internal or external use, and any substances or mixture of substances intended to be used for the cure, mitigation, or prevention of disease of either man or other animals". 34 Stat. 768, 769. One of the significant improvements made by the Federal Food, Drug, and Cosmetic Act in 1938 was the expansion of the definition of "drug". The need for this was pointed out at the very first Senate hearing, Hearing before the Senate Committee on Commerce on S. 1944, 73d Cong., 2d Sess., by the Chief of the Food and Drug Administration. Dunn, *Federal Food, Drug, and Cosmetic Act* (1938), p. 1053. The

first Senate Committee Report, S. Rep. 493, 73d Cong., 2d Sess., on S. 2800, reflected the change. That bill defined "drug" to include "(1) all substances and preparations recognized in the United States Pharmacopoeia, Homoeopathic Pharmacopoeia of the United States or National Formulary or supplements thereto; and (2) all substances, preparations, and devices intended for use in the cure, mitigation, treatment, or prevention of disease in man or other animals; and (3) all substances and preparations, other than food, and all devices intended to affect the structure or any function of the body." S. 2800, Sec. 2(b), Dunn, *supra*, at 72.

The definition was revised in S. 5, 74th Cong., 1st Sess.; S. Rep. 361, 74th Cong., 1st Sess. (March 26, 1935), Dunn, *supra*, at 237, 239, to include substances, preparations and devices intended for diagnostic purposes. S. 5, Sec. 201(b), Dunn, *supra*, at 214. A controversy over this definition developed on the Senate floor, Senator Bennett Clark contending that it was not proper to classify devices as drugs, and that diagnostic devices were so broadly defined as to make even a bathroom scale a drug. Dunn, *supra*, at 286–296. Senator Copeland, the Senate sponsor, proposed an amendment to add a definition of "device", parallel to that for "drug", but the drug definition was unchanged except for that revision. Dunn, *supra*, at 495–496.

Later explanations of the "drug" definition were brief, but they made it clear that Congress knew the definition was a broad one. For example, S. Rep. 2139, 75th Cong., 3d Sess., said: "The definition of drug is

expanded to include articles used in the diagnosis of disease, and articles other than food intended to affect the structure or any function of the body of man or other animals. These expansions are needed to give jurisdiction over a great number of drugs which are not amenable to control under the present law." Dunn, *supra,* at 817.

This history negates the conclusion of the district court that the definition of drug in Section 201(g) was intended by Congress to be restricted to "articles administered to man or other animals, either internally or externally." The term drug was intended to be as broad as necessary to accomplish the general purpose of the Act to protect the health of the nation.

Nothing in the legislative history precludes a reasonable interpretation of the term drug designed to accomplish the evident purpose of Section 507 to assure that any antibiotic used in the treatment of disease in man would be effective for its intended use. In Section 507, Congress required the certification of antibiotic drugs "as necessary to adequately insure safety and efficacy of use." "Efficacy," used here, carries its plain meaning. As explained by Secretary Ribicoff in 1962, in testifying before a House of Representatives committee considering the use of the term in the bill which was eventually enacted as Section 507 (Hearings Before the Committee on Interstate and Foreign Commerce, House of Representatives, 87th Cong., 2d Sess., p. 80):

"[E]fficacy" means that it is effective to do the job that it is represented to do. If it is represented to effect a cure, it will effect such a cure. If it is represented to clear up a condition, it will clear up a condition.

Many drugs on the market might be safe but absolutely useless to effect what they are represented to accomplish.

If antibiotics administered to patients are to be effective, the antibiotic sensitivity discs must also be effective. If, as Congress has determined, batch testing is necessary to insure the efficacy of antibiotic drugs in use, batch testing is equally necessary to insure the efficacy of antibiotic discs. The legislative history supports the view that the term "drug" can and should properly be construed to accomplish that beneficial purpose.

CONCLUSION

For the foregoing reasons, the judgment of the court of appeals should be reversed and the case should be remanded for the entry of an appropriate decree of condemnation.

Respectfully submitted.

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